Received: 16 August 2019 | Accepted: 8 September 2019

DOI: 10.1111/echo.14487

Echocardiography WILEY

Cardiotoxicity in breast cancer treatment: What about left ventricular diastolic function and left atrial function?

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Abstract

Aims: Cardiotoxicity is a possible complication of cancer treatment, particularly with anthracyclines and anti-HER2 drugs. Systolic dysfunction has already been described. Diastolic dysfunction and left atrial function are less studied. We sought to analyze the impact of cardiotoxic treatments on left ventricular diastolic function and left atrial (LA) function.

Methods and Results: Retrospective study of 100 patients (all women, with a mean age of 54 ± 12 years) with three exams in the span of 1 year during treatment for breast cancer. Patients with previous cancer treatment, coronary artery disease, significant valvular disease, and atrial arrhythmias were excluded. Diastolic dysfunction was classified according to international guidelines and left atrial strain was analyzed by two-dimensional speckle tracking. In our sample, 74% received anthracyclines, 83% anti-HER2, and 76% radiation treatment. In the follow-up, 20% developed new or worsening diastolic dysfunction. Age was the only independent predictor (OR 1.93, 95% CI 1.04–3.58, P = .037). In left atrial function, only the contractile function was significantly reduced in 20.8% of the patients and age was also the only independent predictor, but with a protective effect (OR 0.51, 95% CI 0.28–0.91, P = .023).

Conclusions: During breast cancer treatment, 20% of the patients develop new or worsening diastolic dysfunction, being age the main determinant, suggesting higher impact of chemotherapy in older patients. Contractile left atrial function is also compromised but, in this case, age seems to be protective. Our results support a stricter surveillance in older patients together to eventually adjust chemotherapy regimens.

KEYWORDS
breast cancer, chemotherapy, diastolic function, left atrial strain

1 | INTRODUCTION

Breast cancer is one of the most common cancers worldwide. In 2018, there were more than two million new cases, representing 11.6% of all new cancer cases.[1] In terms of cause of death, it represents 6.6% of all deaths from cancer.[1] From 2006 to 2016, the number of deaths from breast cancer increased by 17%, but age-standardized mortality rates decreased by 9.9%.[2] There was also a significant reduction of 12.4% in the mean age-standardized years of life lost rate in countries with high socio-demographic index.[2] Portuguese data showed that in 2015, there were 1683 deaths due to breast cancer with an adjusted mortality rate of 19.3 (per 100 000).[3] Treatment efficacy has been

increasing, and patient's survival and longevity have also improved. Cardiotoxicity is very common in breast cancer treatment, both early and late after treatment, and thus, cardiac surveillance is highly recommended in these patients.[4,5] Speckle-tracking echocardiography (STE) has been validated as a quantitative assessment tool for left ventricular (LV) systolic function in this setting and is currently recommended in the surveillance of these patients during and after cancer treatment.[4] Worsening of LV myocardial deformation is common in breast cancer patients undergoing chemotherapy, and an impaired Global Longitudinal Strain (GLS) in patients with preserved LV ejection fraction is independently associated with increased incidence of chemotherapy-induced cardiotoxicity and is thus an earlier predictor compared to the usual measurement of LV ejection fraction.[4,6]

Diastolic dysfunction is common in patients with cancer, both at baseline and during treatment, mainly related to the age group usually affected with cancer[4]; however, no evidence has shown that treatment should be stopped based on these findings.[4] In fact, diastolic parameters have not yet demonstrated value in predicting subsequent cardiotoxicity.

More recently, GLS by STE has been described for assessment of regional and global left atrial (LA) function.[7] Atrial strain has been evaluated in multiple conditions, such as hypertension, diabetes, heart failure, ischemic and valvular heart disease, and atrial fibrillation, including for assessment of prognostic implications.[8-14]

It was our objective to evaluate in patients submitted to breast cancer treatment, the effect of treatment on LV diastolic function, its prognostic effect in subsequent LV systolic function, and the effects in LA function as assessed by STE.

2 | METHODS

2.1 | Population

Retrospective analysis of all consecutive patients prospectively included in a single-center echocardiographic registry of patients submitted to cardiotoxic agents in the setting of Oncology. Patient inclusion started in 2014, and all patients that performed at least three echocardiograms in the span of 1 year in our laboratory during chemotherapy for breast cancer were included in the present analysis. Patients were excluded if they had a previous cancer treatment (with chemotherapy or radiotherapy), or in case, the treatment was started before the baseline echocardiographic assessment. A previous myocardial infarction, coronary revascularization, significant valvular heart disease, and atrial fibrillation/flutter or pacemaker were also exclusion criteria.

Hypertension was defined by a previous diagnosis or treatment with anti-hypertensive drugs. Diabetes was defined by a previous diagnosis or treatment with anti-diabetic drugs. Obesity was defined by a body mass index above 30 Kg/m^2.

2.2 | Echocardiography

A complete standard echocardiographic study was performed using commercially available systems (Vivid 7™, Vivid 9™, and VividE95™; GE Healthcare). The patient was positioned in left lateral position, and the study was performed with a 3.5 MHz transducer. Left ventricular ejection fraction was assessed with the biplane method of disks (modified Simpson's rule).[15] The following four variables were evaluated for identifying LV diastolic dysfunction: mitral annular e′ velocity (septal and lateral), average E/e′ ratio, LA maximum volume index, and tricuspid regurgitation peak velocity.[16] LA volume was calculated with the biplane algorithm, which includes the 4-chamber and 2-chamber apical views.[15] Diastolic dysfunction was classified according to the European Association of Cardiovascular Imaging (EACVI) guidelines.[16] Left ventricular GLS was analyzed by two-dimensional STE. Images were acquired in the three standard apical views, and the transducer settings of the B-mode image were adjusted to achieve a frame rate of at least 55 frames per second (fps) (preferably set at 60–80 fps). Optimization of endocardial and myocardial definition was obtained by adjusting the gray scale. Images were digitally stored in cineloop format that included three sequential beats and were transferred to a workstation for subsequent offline analysis using the software package EchoPAC™ (version 202, GE Healthcare). The borders of the LV endocardium were manually traced, and additional lines were automatically generated by the program near the epicardium. Speckles were traced during the cardiac cycle, in each frame. Whenever necessary, the region of interest was adjusted manually by the operator. Left ventricular GLS was the average of all 18 segments. Left atrial strain was analyzed offline with the same software and with Q-analysis. Thus, dedicated software for atrial analysis was not used. As recommended, LA longitudinal strain was obtained from an optimized apical 4-chamber view of the LA.[7] The 4-chamber view was optimized in terms of orientation, depth, and gain, avoiding LA foreshortening and allowing visualization of the entire LA throughout the cardiac cycle. The region of interest size and shape was adjusted in order to include the thickness of LA wall. LA delineation was performed in a similar manner as for the LV, and it was manually edited if needed. Endocardial contour was extrapolated across the orifice of pulmonary veins and LA appendage. Reference was placed at the onset of the R-wave (R-R gating). With this specific gating, all strains are positive (Figure 1). There are two peaks that correspond to reservoir function (first peak—εR) and atrial contractile function (second peak—εCT). The difference between reservoir strain and atrial contractile strain values reflect conduit function (εCD). Strain measurements were made by a single operator. Because LA strain analysis is not performed with specific software, additional reproducibility analysis was performed.

Cancer treatment-related cardiac dysfunction (cardiotoxicity) was defined by a reduction of 10% points in LV ejection fraction to a value below 50% (lower limit of normal) or by a relative percentage reduction of more than 15% of LV GLS from baseline.[4] Because there are no cutoffs for LA cardiotoxicity, we considered significant a reduction in the LA functional strain parameters above 15% to a value below the 10th percentile (calculated in the baseline evaluation) for each atrial function strain parameter.

All patients gave their informed consent to be included in the registry, and the study complies with the Helsinki declaration.

2.3 | Statistical analysis

Assuming that 5% and 10% of the pairs have diastolic dysfunction in the first and second observation, respectively, that the correlation between paired observations is at least 70%, and applying continuity correction, the study would require a sample size of 68 pairs to achieve a power of 80% and a two-sided significance of 5% to detect a difference of 0.10 between marginal populations. For that reason, 100 patients are our ideal sample size. For LA strain analysis, with a smaller sample of 75 individuals (assuming that in 25% of the patients it would not be possible to evaluate LA strain), with the same power and level of significance, assuming a correlation of 0.85 for LA strain parameters, we obtain an effect size of 1.796.

Continuous variables are expressed as mean and standard deviation. Normality and homogeneity of variance were tested with Kolmogorov-Smirnov′s test and Levene's test, respectively. Categorical variables are reported as absolute frequencies and percentages. Differences between groups for categorical variables were tested with the chi-square test or Fisher′s exact test, as appropriate. For continuous variables, paired Student's *t* test was used.

Multivariate logistic regression models were used to assess the factors associated with LV diastolic dysfunction and LA dysfunction. Factors that remained significant at the 0.10 level in univariate analysis were considered to be significant contributors and were included in the final models. Multicollinearity was also assessed and when identified, those variables were removed from the final multivariate model. Estimates of the association between predictors and endpoints are presented as odds ratio (OR) with 95% confidence interval (CI). The model's calibration was assessed with the Hosmer-Lemeshow test.

To establish and quantify reproducibility of LA strain analysis, agreement and intra- and inter-observer reproducibility were assessed using the interclass correlation coefficient and reliability coefficients (Cronbach's alpha) with two-way mixed effects models. Mean differences and limits of agreement were analyzed with Bland-Altman plots. Twenty-five consecutive patients were selected for reproducibility analysis, and the two operators were blinded for patient status and previous results.

IBM SPSS Statistics Software, version 19.0.0.2 (IBM SPSS Inc) was used for all statistical analysis. All statistical tests were two-sided with a critical value of 0.05 for statistical significance.

3 | RESULTS

3.1 | Population

From an initial sample of 111 patients, 11 were excluded due to previous cancer treatment and the final sample included 100 patients, all females, with a mean age of 54 ± 12 years (28–83 years). The time interval between the first and second exam was 5.7 ± 1.8 months, and the third exam was performed 11.5 ± 2.3 months after the baseline. Baseline characteristics and cancer treatment are detailed in Table 1. All patients had a baseline LV ejection fraction > 50% and LV GLS > −18.5%. During treatment, three patients developed LV systolic dysfunction as assessed by LV ejection fraction and 24 patients by LV GLS. Regarding treatment, the most commonly used chemotherapy regimens were as follows: FEC × 3 (5-fluorouracil, Epirubicin, Cyclophosphamide, with a maximum total dose of 300 mg/m^2 of epirubicin) followed by DTP × 3 (Doctaxel, Traztuzumab, Pertuzumab); AC × 4 (Doxorubicin, Cyclophosphamide, with a maximum total dose of 240 mg/m^2 of doxorubicin) followed by DT × 4 (Docetaxel + Trastuzumab); TCH × 6 (Docetaxel, Carboplatin, Trastuzumab). In 81% of cases, these regimens were followed by 1 year of trastuzumab alone every 21 days in the dose of 6 mg/Kg. Radiation treatment occurred at a median of 5 months after the baseline echocardiogram, and for that reason, the implications in LV diastolic function and LA function in the second echocardiographic evaluation were not analyzed.

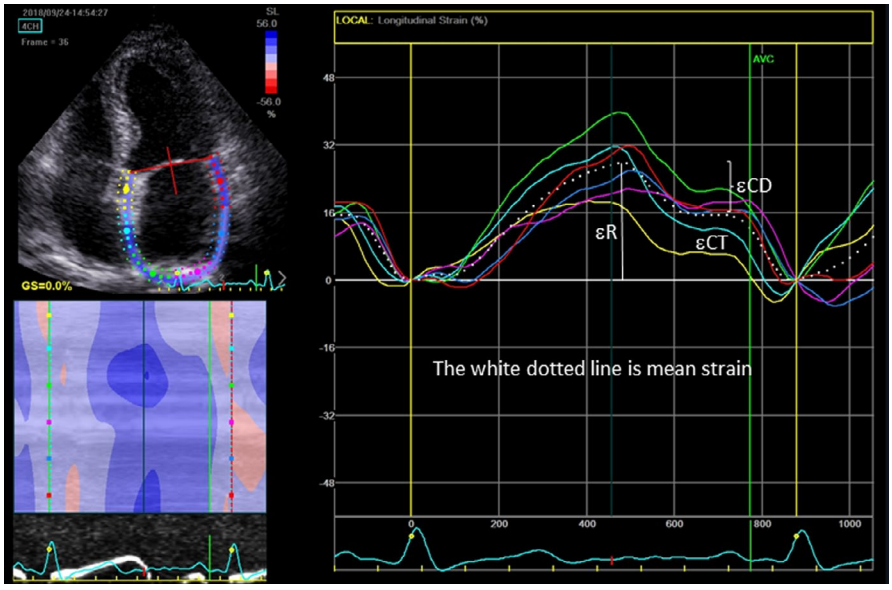

FIGURE 1 Left atrial strain analysis by speckle-tracking echocardiography. εCD = conduit strain; εCT = contractile strain; εR = reservoir strain

TABLE 1 Baseline characteristics and cancer treatment during the study

Cardiovascular risk factors n (%)	
Hypertension	33 (33.0)
Obesity	30 (30.0)
Diabetes	12 (12.0)
Chemotherapy (%)	
Anthracylines	74 (74.0)
Doxorubicin	53 (53.0)
Epirubicin	21 (21.0)
Cyclophosphamide	78 (78.0)
Docetaxel	80 (80.0)
Paclitaxel	11 (11.0)
Anti-HER2	83 (83.0)
Trastuzumab	81 (81.0)
Pertuzumab	17 (17.0)
Aromatase inhibitors	23 (23.0)
5—Fluorouracil	24 (24.0)
Metotrexate	3 (3.0)
Carboplatin	9 (9.0)
Goserelin	7 (7.0)
Tamoxifen	49 (49.0)
Anthracyclines + Anti-HER2	56 (56.0)
Trastuzumab + Pertuzumab	17 (17.0)
Neoadjuvant chemotherapy (%)	32 (32.0)
Radiation treatment (%)	76 (76.0)

Abbreviations: HER = human epidermal growth factor receptor.

3.2 | Left ventricular diastolic function

During follow-up, there was a significant increase in LA volume (Table 2). In regard to diastolic function, there was a steady worsening from the baseline to the third echo examination (Table 2). In total, 20 patients developed new or worsening diastolic dysfunction during treatment. In an exploratory analysis, the main potential predictors were age, hypertension, docetaxel use, and aromatase inhibitors use (Table 3). However, in multivariate analysis, only age remained as an independent predictor of diastolic dysfunction development. Neither anthracyclines use (OR 0.78, 95% CI 0.26–2.29), Anti-HER2 use (OR 0.45, 95% CI 0.15–1.40), nor both (OR 0.44, 95% CI 0.16–1.21), nor radiation therapy (OR 1.44, 95% CI 0.38–5.57—comparison only for the third exam) nor LV systolic dysfunction development (OR 1.20, 95% CI 0.41–3.54) was associated with LV diastolic dysfunction development/worsening during chemotherapy treatment.

In patients with baseline diastolic dysfunction, the risk of development of systolic cardiotoxicity during the 12 months follow-up was not significant (OR 2.03, 95% CI 0.39–10.66). Patients with normal LV systolic function in the second exam but that developed new or worsening diastolic dysfunction did not have an increased risk of cardiotoxicity in the third exam (OR 2.31, 95% CI 0.51–10.45).

There were no heart failure hospitalizations. In 37% of the patients, mild fatigue was reported and mild pedal edema in 7%. However, fatigue is a commonly reported side effect of chemotherapy and in most cases unrelated to heart failure. There was no association between fatigue and left ventricular diastolic dysfunction (only 35% of the patients with fatigue had diastolic dysfunction, $P = .836$), and the same was observed for peripheral edema (10% of the patients with edema had diastolic dysfunction, $P = .625$). There was, however, some association, as expected, with left ventricular systolic dysfunction (100% of patients with systolic dysfunction had fatigue, $P = .048$; 33% of the patients with systolic dysfunction had edema, $P = .197$).

3.3 | Left atrial function assessment

Reproducibility analysis showed excellent reproducibility both for intra- and inter-observer, despite the use of a nondedicated software for LA strain analysis (Table S1). It was possible to assess LA strain in 77 patients (53 ± 12 years). Risk factors and treatment proportions are similar to the main study group, as well as the time interval between studies. In this sample, it was also observed an increase in LA volume and LV systolic dysfunction during follow-up (Table 4). However, we did not observe any significant worsening of mean left atrial function as assessed by strain analysis. The selected cutoff for εR was 16.8%, 8.0% for εCT, and 7.1% for εCD. The parameter that had more important worsening during treatment was εCT (Table 5). No factor was independently associated with εR or εCD reduction (Table 6). For εCT, it was only age that showed an inverse relationship. There was also a trend to be independently associated with baseline LV ejection fraction.

4 | DISCUSSION

During the first year of breast cancer treatment, there is a significant worsening in diastolic function, being age the only independent predictor. Neither baseline diastolic dysfunction nor LV systolic dysfunction had any significant impact on LV diastolic dysfunction. Regarding LA function, the contractile function was the one that was more frequently compromised, being age a protective factor.

In breast cancer treatment, most regimens include the use of anthracyclines, taxanes, and inhibitors of human epidermal growth factor receptor 2 (anti-HER2) drugs, which are associated with LV dysfunction.[4] Anthracyclines can induce early cardiotoxicity due to cell necrosis (type I toxicity) and consequent myocardial dysfunction.[5] It causes irreversible cardiac damage and progressive cardiac remodeling as a late consequence.[4,5] The most common hypothesis is the generation of reactive oxygen species, and lipid peroxidation of the cell membrane that damages the cardiomyocyte.[4,5] These agents have a cumulative dose relationship with cardiotoxicity. When a cumulative lifetime dose of doxorubicin (or equivalent) exceeds 400 mg/m^2, the incidence of heart failure is up to 5%.[4,5] However, there is considerable variability among patients in their susceptibility.[4] Early effects occur within the first year of treatment in about 98% of the cases.[4] Currently, the doses in routine clinical

TABLE 2 Echocardiographic results for diastolic function

Variable	Echo 1	Echo 2	*P*-value	Echo 3	*P*-value (2 vs 3)	*P*-value (1 vs 3)
Mitral E (cm/s)	76 ± 19	78 ± 18	.249	76 ± 18	.240	1.000
Mitral A (cm/s)	75 ± 19	76 ± 18	.691	74 ± 18	.292	.565
Mitral E/A	1.0 ± 0.4	1.1 ± .3	.491	1.1 ± 0.3	.622	.799
Mitral DecT (m/s)	209 ± 52	191 ± 40	.060	191 ± 54	.996	.018
Mitral E′s (cm/s)	8.2 ± 2.6	8.1 ± 2.4	.822	8.1 ± 2.4	1.000	.568
Mitral E′l (cm/s)	11.4 ± 3.2	11.2 ± 3.2	.445	11.0 ± 3.2	.214	.310
Mitral E′ mean (cm/s)	9.9 ± 2.6	9.7 ± 2.7	.441	9.6 ± 2.5	.509	.290
E/E′	8.1 ± 2.4	8.5 ± 2.3	.177	8.3 ± 2.6	.651	.311
TR vel (m/s)	2.3 ± 0.3	2.4 ± 0.3	.490	2.4 ± 0.3	.097	.454
LA/BSA (mL/m^2)	24 ± 7	25 ± 7	.115	27 ± 9	.100	.003
LVEF (%)	64 ± 6	62 ± 7	.004	61 ± 7	.424	<.001
LV GLS (%)	−20.0 ± 3.2	−19.0 ± 3.0	.031	−18.6 ± 2.6	.256	.001
Diastolic dysfunction (%)			.217		.077	.030
Normal	94	88		84		
Grade 1	6	12		11		
Grade 2	0	0		5		

Abbreviations: BSA = body surface area; DecT = deceleration time; LA = left atrial; LVEF = left ventricular ejection fraction; LVGLS = left ventricular global longitudinal strain; TR = tricuspid regurgitation.

TABLE 3 Logistic regression analysis for predictors of left ventricular diastolic dysfunction development

	Univariate		Multivariate	
Variable	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age (per 10-y increase)	2.79 (1.65–4.71)	<.001	1.93 (1.04–3.58)	.037
Hypertension	7.49 (2.53–22.2)	<.001	2.74 (0.74–10.19)	.132
Docetaxel	0.36 (0.12–1.08)	.068	0.49 (0.13–1.89)	.301
Aromatase inhibitor	3.86 (1.35–11.06)	.012	2.04 (0.59–7.12)	.262

use were reduced, and typical cumulative exposure is now mostly in the 240–360 mg/m^2 range for doxorubicin and 450–600 mg/m^2 for epirubicin.[5] Cyclophosphamide cardiotoxicity is relatively rare, and it occurs within days of drug administration, with the same risk factors as for anthracyclines.[4] Docetaxel, used frequently in combination with or after anthracyclines, cyclophosphamide or trastuzumab, also increases the incidence of heart failure.[4] Taxanes also reduce doxorubicin elimination, resulting in higher plasmatic levels.[4] In this regard, paclitaxel is more cardiotoxic that docetaxel. Anti-HER2 drugs, such as trastuzumab and pertuzumab, can be given concomitantly with anthracyclines, but due to the high incidence of cardiotoxicity, it is more commonly used after anthracyclines or using an anthracycline-free chemotherapy regimen with antimetabolites or alkylating agents.[4] In contrast to other agents, trastuzumab toxicity manifests during treatment and unlike anthracyclines, long-term studies are reassuring in terms of absence of late effects and it is not cumulative dose-related.[4] A drug-free interval between the two agents is recommended.[4,5] With this drug, cardiac dysfunction appears to rise from impairment of contractility due to cell dysfunction (type II toxicity) rather than loss of myocytes and is potentially reversible.[5]

Regarding radiotherapy, there is a longtime delay between exposure and clinical manifestation of radiation-induced cardiotoxicity and it results from marked interstitial myocardial fibrosis.[4] Also, continuous improvements in radiation techniques are reducing its incidence.[4] In general, the main risk factors for cardiotoxicity are the cumulative dose of some drugs (such as anthracyclines), age above 65 years, preexisting cardiac diseases leading to increased wall stress, arterial hypertension, concomitant use of mediastinal radiation and/or a concomitant or incorrect timing of administration of multiple cancer drugs (alkylating, antimicrotubule agents, and particularly immunotherapy and targeted therapies) with potential for cardiotoxic effects from interactions among the different therapeutic modalities.[4,5]

If all these drugs have an effect on LV myocyte, they can also induce diastolic dysfunction (that can potentially be used as an earlier indicator of progressive LV systolic dysfunction), or LA dysfunction. However, diastolic parameters have not yet demonstrated value in predicting subsequent chemotherapy-related cardiotoxicity. E/e′ ratio

TABLE 4 Echocardiographic results for the left atrial analysis

Variable	Echo 1	Echo 2	*P*-value	Echo 3	*P*-value (2 vs 3)	*P*-value (1 vs 3)
Mitral E (cm/s)	76 ± 20	77 ± 20	.379	75 ± 19	.168	.641
Mitral A (cm/s)	75 ± 19	74 ± 17	.617	73 ± 18	.584	.271
Mitral E/A	1.1 ± 0.4	1.1 ± 0.3	.673	1.1 ± 0.3	.460	.817
Mitral DecT (m/s)	208 ± 48	192 ± 42	.026	193 ± 58	.898	.082
Mitral E′s (cm/s)	8.1 ± 2.7	8.2 ± 2.4	.629	8.0 ± 2.4	.281	.464
Mitral E′l (cm/s)	11.5 ± 3.1	11.3 ± 3.2	.627	11.0 ± 3.2	.257	.217
Mitral E′ mean (cm/s)	9.9 ± 2.6	9.8 ± 2.6	.882	9.6 ± 2.5	.199	.227
E/E′	8.1 ± 2.4	8.3 ± 2.3	.425	8.3 ± 2.7	.866	.473
TR vel (m/s)	2.3 ± 0.3	2.3 ± 0.3	.716	2.4 ± 0.3	.432	.730
LA/BSA (mL/m^2)	24 ± 7	25 ± 7	.563	27 ± 9	.044	.014
LVEF (%)	64 ± 7	62 ± 7	.011	60 ± 7	.139	<.001
LV GLS (%)	−19.7 ± 3.3	−19.0 ± 3.0	.177	−18.6 ± 2.5	.422	.017
Diastolic dysfunction n(%)			1.000		.084	.060
Normal	72 (93.5)	71 (92.2)		64 (83.1)		
Grade 1	5 (6.5)	6 (7.8)		9 (11.7)		
Grade 2	0	0		4 (5.2)		
LA strain (%)						
εR	30.8 ± 11.3	31.3 ± 10.2	.741	30.5 ± 10.9	.601	.822
εCT	13.2 ± 4.5	13.0 ± 4.3	.818	12.5 ± 4.5	.409	.286
εCD	17.7 ± 8.7	18.2 ± 8.5	561	18.0 ± 8.6	.827	.753

Abbreviations: εCD = LA conduct strain; εCT = LA contractile strain; εR = LA reservoir strain; BSA = body surface area; DecT = deceleration time; LA = left atrial; LVEF = left ventricular ejection fraction; LVGLS = left ventricular global longitudinal strain; TR = tricuspid regurgitation.

TABLE 5 Significant changes in left atrial strain parameters

n (%)	Reduction 1–2	Reduction 2–3	Reduction 1–3	Total reduction
εR	3 (3.9)	8 (10.4)	7 (9.1)	11 (14.3)
εCT	8 (10.4)	9 (11.7)	8 (10.4)	16 (20.8)
εCD	7 (9.1)	6 (7.8)	4 (5.2)	13 (16.9)

Abbreviations: εCD = LA conduit strain; εCT = LA contractile strain; εR = LA reservoir strain.

remains questionable in the oncology setting because there might be E velocity fluctuations as a consequence of changes in loading conditions associated to side effects of chemotherapy (nausea, vomiting, and diarrhea) and not as a result of real change in left ventricular diastolic performance.[17] In this regard, e′ is more independent of preload.[17] In our sample, we demonstrated a significant worsening of diastolic function during treatment. However, the main determinant of worsening was age and this is in accordance with previous observations of LV systolic cardiotoxicity being more frequent in patients older than 65 years.[4] We can conclude that these agents are more detrimental in older individuals, and thus, a more strict surveillance should be undertaken in those patients for early detection of those changes and to decide on the need to use less aggressive regimen. In our sample, we also did not observe a significant relationship between diastolic dysfunction development/worsening and LV systolic dysfunction during follow-up, and for that reason, no recommendations about treatment interruption can be suggested.

Left atrial indexed volume remains the main echocardiographic parameter to assess the remodeling and indirectly the function of the LA and is a powerful prognostic tool.[17-20] However, volumetric measures of LA function are limited by lower sensitivity in early disease states and can be increased due to other diseases.[19] LA myocardial analysis using 2DSTE identifies LA dysfunction despite normal LA ejection fraction and normal LA indexed volume in patients with LV diastolic dysfunction.[17] Thus, myocardial LA analysis using 2DSTE has several advantages over volumetric LA measurements. The advantages of left atrial strain by STE are the rapid and easy performance, angle independence, it is less affected by side lobes, reverberations and dropout artifacts, the possibility of offline processing, and provides qualitative assessment of LA function.[17] The main disadvantages are the frame rate dependence, the potential errors in epicardial/endocardial border tracing and the absence of a dedicated analysis software.[17] Unlike LV strain, LA strain using STE has not been validated, but there is a growing body of outcome data supporting its diagnostic and prognostic value.[8-14] Our results showed very good reproducibility with the technique.

LA strain parameters are usually higher in women, compared to men.[21] With increasing age, it decreases progressively, being more pronounced in women, and independently of baseline characteristics such

TABLE 6 Factors associated with left atrial strain parameters significant changes

	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Significant εR change				
Docetaxel	0.21 (0.06–0.84)	.027	0.26 (0.06–1.10)	.067
Diastolic dysfunction	3.20 (0.79–12.98)	.100	2.19 (0.45–9.89)	.307
Significant εCD change				
Hypertension	3.81 (1.11–13.10)	.034	2.34 (0.51–10.82)	.277
Docetaxel	0.30 (0.08–1.09)	.068	0.40 (0.10–1.64)	.201
Anastrazol	4.30 (1.01–18.26)	.048	2.78 (0.55–13.94)	.213
Diastolic dysfunction	3.82 (1.02–14.31)	.047	1.34 (0.23–7.68)	.741
Significant εCT change				
Age (per 10-y increase)	0.55 (0.32–0.95)	.031	0.51 (0.28–0.91)	.023
Baseline LVEF	1.08 (0.99–1.18)	.066	1.11 (1.00–1.23)	.055
Pertuzumab	3.06 (0.91–10.34)	.072	2.31 (0.49–10.85)	.287
Neoadjuvant chemotherapy	3.94 (1.25–12.41)	.019	2.68 (0.66–10.95)	.170

Abbreviations: εCD = left atrial conduit strain; εCT = left atrial contractile strain; εR = left atrial reservoir strain; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio.

as blood pressure, LA volume or LV diastolic function.[17-21] With increasing age, impaired LV relaxation reduces passive atrial conduit function and LA stiffness decreases reservoir function, limiting LV filling.[21] With senescence, LA contraction augments as a compensatory mechanism with a late decrease with further aging.[21] The same changes are reported with LV diastolic dysfunction.[22,23] In early stages, LA reservoir and conduit strain decreases and an increase in its booster function can compensate filling. But with prolonged dysfunction, LA dilation occurs, and eventually, LA mechanical function shows a fall in the relative contribution of LA pump to LV filling. This is particularly important for heart failure with preserved ejection fraction progression because LA strain parameters are independently associated with abnormal exercise hemodynamics.[24] Some authors suggest the use of LA reservoir strain (peak LA strain) as a promising prognostic marker in heart failure.[25]

Our baseline values for all strain parameters, with the exception of εCD, were lower in comparison with the normal values reported in the literature.[19] Our explanation is the difference in baseline characteristics of our sample in comparison with the healthy subjects analyzed in the meta-analysis that defined normal LA strain values. Reference values for LA strain were defined for patients without cardiovascular risk factors. Our sample has several patients with an age > 60 years, hypertension and baseline diastolic dysfunction that was not present in the previous meta-analysis.

We observed a substantial reduction in LA contractile function in more than 20% of the patients, although all other parameters were also changes but in fewer patients. The reduction in contractile function was only independently associated with age, being in that case protective. As previously mentioned, age is one of the most important predictors of LA dysfunction, independently of other characteristics such as LV diastolic dysfunction and as such, our results are in accordance with previous reports. Thus, the most likely explanation is that, as previously mentioned, εR and εCD usually deteriorate with increasing age, but contractile function is positively correlated with age (increases with age).[19,21] Augmented LA active contraction occurs as a compensatory mechanism with senescence.[19,21] For that reason, in older patients, we expect a less significant or delayed decrease in LA contractile function by strain analysis, justifying the inverse independent association observed.

4.1 | Limitations

Although our sample size is adequate according to our sample size analysis, it is, nonetheless, relatively small. For that reason, our results require confirmation in larger samples.

This is a retrospective study, and strain measurements were not a prespecified test in routine evaluation. Thus, a significant number of patients did not have adequate images for strain analysis. Our feasibility was 77%, a little lower compared to other studies that report exclusion rates around 15% due to poor image quality. In our case, the main reason was inadequate storing of images and not image quality.

Intervendor variability is a problem previously reported in strain analysis with speckle tracking. However, in the previously mentioned meta-analysis for the LA strain reference values, they found no significant differences between vendors.[19]

Another potential limitation of left atrial strain is LA wall thinness, with the possibility of wall dropout and poor tissue tracking.

5 | CONCLUSION

In our sample of women with breast cancer, during the first year of breast cancer treatment, there is a significant worsening in diastolic function, being age the only independent predictor. Neither baseline diastolic dysfunction nor LV systolic dysfunction had any

significant impact on LV diastolic dysfunction. Regarding LA function, the contractile function was the one that was more frequently compromised, being age the only independent predictor, but as a protective factor.

CONFLICT OF INTERESTS

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Reproducibility analysis for left atrial strain by 2-dimensional speckle tracking echocardiography.

How to cite this article: Timóteo AT, Moura Branco L, Filipe F, et al. Cardiotoxicity in breast cancer treatment: What about left ventricular diastolic function and left atrial function?. *Echocardiography*. 2019;36:1806–1813. https://doi.org/10.1111/echo.14487